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The role of acute cortisol and DHEAS in predicting acute and chronic PTSD symptoms

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KEYWORDS
Posttraumatic stress disorder;
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Prospective study

Summary
Background: Decreased activation of the hypothalamus—pituitary—adrenal (HPA) axis in response to stress is suspected to be a vulnerability factor for posttraumatic stress disorder (PTSD). Previous studies showed inconsistent findings regarding the role of cortisol in predicting PTSD. In addition, no prospective studies have examined the role of dehydroepiandrosterone (DHEA), or its sulfate form DHEAS, and the cortisol-to-DHEA(S) ratio in predicting PTSD. In this study, we tested whether acute plasma cortisol, DHEAS and the cortisol-to-DHEAS ratio predicted PTSD symptoms at 6 weeks and 6 months post-trauma.
Methods: Blood samples of 397 adult level-1 trauma center patients, taken at the trauma resuscitation room within hours after the injury, were analyzed for cortisol and DHEAS levels. PTSD symptoms were assessed at 6 weeks and 6 months post-trauma with the Clinician Administered PTSD Scale.
Results: Multivariate linear regression analyses showed that lower cortisol predicted PTSD symptoms at both 6 weeks and 6 months, controlling for age, gender, time of blood sampling, injury, trauma history, and admission to intensive care. Higher DHEAS and a smaller cortisol-to-DHEAS ratio predicted PTSD symptoms at 6 weeks, but not after controlling for the same variables, and not at 6 months.
Conclusions: Our study provides important new evidence on the crucial role of the HPA-axis in response to trauma by showing that acute cortisol and DHEAS levels predict PTSD symptoms in survivors of recent trauma.

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1. Introduction

Injury victims presenting to an emergency room have an increased risk of developing trauma-related psychopathology, such as posttraumatic stress disorder (PTSD). Prevalence rates of PTSD following a traffic accident, one of the most common injury causing traumatic events (de Vries and Olff, 2009), vary greatly, from 8–45% at 1 month to 7–26% at 12 months (for a review, see Heron-Delaney et al., 2013). To explain why some develop PTSD and others do not, studies have examined the role of the hypothalamus–pituitary–adrenal (HPA) axis (Delahanty et al., 2000, 2003, 2005; McFarlane et al., 1997, 2011; Resnick et al., 1995, 1997; Shalev et al., 2008; Yehuda et al., 1998b). It has been hypothesized that an insufficient activation of the HPA-axis in response to stress serves as vulnerability for PTSD (Yehuda et al., 1998a; Yehuda, 2002). During acute stress, the hypothalamus secretes corticotrophin-releasing hormone. This in turn stimulates the pituitary gland to release adrenocorticotropic hormone, which leads to the production of glucocorticoids (cortisol) and dehydroepiandrosterone (DHEA) by the adrenal cortex (Vinson et al., 2007). Cortisol suppresses metabolic, immuno- and neurodefensive processes to adequately cope with the stressor, and triggers a negative feedback loop when sufficient circulating levels are reached. Low levels of circulating cortisol have been found to be a vulnerability factor for developing PTSD symptoms, either directly (Delahanty et al., 2003) or indirectly through prior trauma exposure (Resnick et al., 1995; Yehuda et al., 1998b). They fail to trigger the negative feedback loop, thus prolonging the adrenergic response, which may exacerbate consolidation of the traumatic memory. This may lead to intrusive symptoms, which may increase the risk for PTSD (Yehuda, 2002).

Whereas high cortisol has catabolic properties, DHEA and its sulfate form DHEAS have been found to possess anabolic, neuroprotective and antiglucocorticoid effects, showing neurogenerative effects in the hippocampus (Karishma and Herbert, 2002) and protection against the neurotoxic effects of cortisol in studies in rodents (Kaminska et al., 2000; Kimonides et al., 1998, 1999). This may contribute to an upregulation of HPA-axis responses as well as mitigate possible deleterious effects of high cortisol levels on the brain in PTSD (Rasmusson et al., 2003). As such, it may be hypothesized that dysregulations in the HPA-axis function associated with PTSD may also be evident in an abnormal DHEA-response. DHEAS is much more abundant than DHEA, because DHEAS has longer half-life and lower clearance (Lennartsson et al., 2012). Because DHEAS levels are also more stable and show no diurnal variation (Kroboth et al., 1999), they are often preferred in studies on long term effects of stress. Studies on acute stress, on the other hand, often assess DHEA, since DHEAS serves as a reservoir for DHEA biosynthesis and DHEA rather than DHEAS is expected to respond to acute psychosocial stress (Izawa et al., 2008; Morgan et al., 2004; Oberbeck et al., 1998; Pico-Alfonso et al., 2004; Shirotsuki et al., 2009). However, in a recent study, although the response of DHEA was more pronounced, both DHEA and DHEAS were found to increase in response to acute psychosocial stress (Lennartsson et al., 2012). In addition, DHEAS was found to increase in response to low, but not high, intensity military stress exposure (Morgan et al., 2004; Taylor et al., 2007). Cortisol and DHEA(S) are often addressed as a ratio, representing the balance between anabolic and catabolic hormones (Maninger et al., 2009). A high ratio of cortisol-to-DHEA(S), or conversely a low DHEA(S)-to-cortisol ratio, represents a catabolic balance. A low cortisol-to-DHEA(S) ratio, or a high DHEA(S)-to-cortisol ratio, reflects an anabolic balance. A higher cortisol-to-DHEA ratio has been linked to a chronic stress response in depressed adolescents and adults (Goodyer et al., 1998; Young et al., 2002), as well as more resilient functioning in both maltreated and non-maltreated children (Cicchetti and Rogosch, 2007), whereas a higher DHEAS-to-cortisol ratio was positively correlated with fewer dissociative symptoms after prolonged and extreme training stress (Morgan et al., 2004; Taylor et al., 2007). Thus, previous findings are inconclusive with respect to the role of the cortisol-to-DHEA(S) ratio in the onset of psychiatric disorders such as PTSD.

Findings from prospective studies on acute cortisol levels as a predictor for PTSD so far are inconsistent. Some studies have found that low cortisol levels immediately or in the first days following trauma predict PTSD diagnosis (Delahanty et al., 2000; McFarlane et al., 1997) or symptoms (Aardal-Eriksson et al., 2001; Ehring et al., 2008; McFarlane et al., 2011). In some of these studies, however, the association disappeared when controlling for possible confounding variables, such as injury severity and history of PTSD (Delahanty et al., 2000), and time of the accident or blood sampling (McFarlane et al., 1997). Other studies found no direct relationship between initial cortisol and subsequent PTSD (Bonne et al., 2003; McFarlane et al., 1997; Resnick et al., 1995; Shalev et al., 2008). Variations in methodology, for example, when (i.e., immediately post-trauma up to several days after the event) or how (i.e., saliva, urine or plasma) cortisol was measured, might explain these differences. Lack of power due to a small sample size has been referred to by some studies as a possibility for not finding a significant association (Delahanty et al., 2000; Ehring et al., 2008). Therefore, it has been argued that the predictive effect of cortisol should be replicated in large, consecutively recruited samples, taking into account the important confounders. Until now, no prospective studies examining whether the DHEA or DHEAS response is implicated in the development of PTSD have been carried out yet.

In this study, we investigated whether plasma cortisol, DHEAS and cortisol-to-DHEAS ratio, collected immediately following traumatic injury, predicted PTSD symptoms at 6 weeks and 6 months post-trauma in a sample of 397 acutely injured trauma victims. We hypothesized that lower levels of cortisol predict greater PTSD symptoms at 6 weeks and 6 months. Although the role of DHEAS in the development of PTSD is yet unclear, we also expected that lower levels of DHEAS and a smaller cortisol-to-DHEAS ratio predict PTSD symptoms at 6 weeks and 6 months.

2. Methods and materials

2.1. Subjects and procedure

Patients were recruited between 2005 and 2009 as part of a large ongoing prospective study of psychopathology following

injury. Injury patients presented by the ambulance service at two academic level-1 trauma centers in Amsterdam, The Netherlands, were consecutively included, if they met inclusion criteria of age (18 years and older), having sustained injuries from a traumatic event (cf. A1-criterion of the DSM IV PTSD diagnosis), and mastery of the Dutch language. Patients with injuries due to deliberate self-harm, with an organic brain condition, current psychotic symptoms or disorder, bipolar disorder, depression with psychotic features, with moderate to severe traumatic brain injury (i.e., Glasgow Coma Scale (GCS) score of less than 13) (Teasdale and Jennett, 1974), or who permanently resided outside the Netherlands, were excluded. Medical ethical approval was obtained from the institutional review boards of the Academic Medical Center and Vrije Universiteit medical center. Upon arrival at the trauma center and at initial medical examination, medical staff collected blood samples for stress hormone assessment. Research assistants selected eligible patients from the hospitals' registrations and contacted them within 72 h of the injury in-hospital or by telephone for participation. Patients provided verbal and written informed consent for the psychological assessments and to analyze the collected blood samples for stress hormones. All clinical assessments were performed at the Center for Anxiety Disorders of the Academic Medical Center, at bedside or at the private home of the patient by trained master and bachelor level psychologists (for more details, see Mouthaan et al., 2011).

2.2. Measures

2.2.1. Cortisol and DHEAS

A 4.5 mL cryovial of blood was stored at −80 °C immediately after collection by the trauma center staff at the patient's initial medical assessment. Cortisol and DHEAS levels (in nmol/L) were analyzed in batch. Cortisol was analyzed by a chemiluminiscence assay using the Immulite 2000 (Siemens, Breda, The Netherlands) with inter-assay and intra-assay coefficients of variation 5.5 and 8.3%. DHEAS was measured by RIA (Siemens) with inter-assay and intra-assay coefficients of variation 4.4 and 6.3%. Reference values for cortisol levels were 220—650 nmol/L for 8:00 h AM and 100—450 nmol/L for 16:00 h PM. Reference values for DHEAS levels were: 8—17 nmol/L for men below age 30, 2—10 nmol/L for women below age 30, 3—14 nmol/L for men age 30—50, 1—7 nmol/L for women age 30—40, .9—7 nmol/L for women age 40—50, 2—8 nmol/L for men age 50—60, .7—5 nmol/L for women age 50—60, 1—8 nmol/L for men age 60—70, .4—4 nmol/L for women age 60—70, .8—5 nmol/L for men age 70—80 and .2—1 nmol/L for women age 70—80. Time of day of blood sampling was registered for each patient. Cortisol-to-DHEAS ratio was computed by dividing cortisol levels by DHEAS levels. A smaller cortisol-to-DHEAS ratio indicated lower cortisol relative to higher DHEAS levels, whereas a higher ratio indicates higher cortisol levels relative to lower DHEAS.

2.2.2. Injury-related characteristics

Injury severity was assessed using the Injury Severity Score (ISS), a scoring system that provides an overall severity score for patients with traumatic injuries. The ISS ranges from 0 (no injury) to 75 (unsurvivable injury) with a score of 16 and higher indicating severe injury (Copes et al., 1990). The Glasgow Coma Scale (GCS) is a neurological scale to record level of consciousness and consists of three parameters: Best Eye Response (four grades), Best Verbal Response (five grades), Best Motor Response (six grades). Resulting scores are between 3 (deep unconsciousness) and 15 (fully conscious) (Teasdale and Jennett, 1974). Both ISS and GCS were assessed by the treating physician at initial medical examination, and were later generated from the hospital trauma registration systems.

2.2.3. Posttraumatic stress disorder

The Clinician Administered PTSD Scale (CAPS) (Blake et al., 1995) was used to assess PTSD symptoms at 6 weeks and 6 months. The CAPS is a 30-item semi-structured interview for diagnosing PTSD (Weathers et al., 2001). Symptom severity is determined by adding frequency and intensity of the 17 symptoms of intrusion, avoidance and hyperarousal (both ranging from 0 to 4, total scores ranging from 0 to 136). The rule of Weathers et al. (1999) was used to establish a PTSD diagnosis, in which symptoms need at least a frequency of 1 and intensity of 2 with a total score of at least 45 points.

2.2.4. Analyses

As part of a longitudinal database with multiple repeated PTSD assessments, missing data of continuous CAPS outcomes were replaced using multiple imputation (SPSS 21.0), creating five different datasets. In this procedure, the fully conditional specification approach was used, in which data were imputed on a variable-by-variable basis by specifying an imputation model per variable. This method has been found to work well in practice (van Buuren, 2011). Independent samples *t*-tests and chi-square tests were used to determine significant associations between demographics and injury-related characteristics and cortisol, DHEAS and cortisol-to-DHEAS ratio. For Pearson correlations and multivariate linear regression analyses, CAPS scores and values for cortisol, DHEAS and cortisol-to-DHEAS ratio were positively skewed and were square root-transformed.

We specified 8 separate multivariate linear regression models for predicting PTSD symptoms. We analyzed whether independent variables cortisol and DHEAS predicted PTSD symptoms at 6 weeks (model 1) and 6 months (model 3). We added gender, age, time of blood sampling, injury severity, trauma history, and ICU admission as covariates to control for possible confounding effects in models 2 (for 6 weeks PTSD) and 4 (for 6 months PTSD). The same procedures were repeated for cortisol-to-DHEAS ratio as independent variable. In models 5 and 7, we tested whether cortisol-to-DHEAS ratio predicted PTSD symptoms at 6 weeks (model 5) and 6 months (model 7). We added the above mentioned covariates gender, age, time of blood sampling, injury severity, trauma history, and ICU admission to control for possible confounding effects (model 6 with PTSD symptoms at 6 weeks and model 8 with PTSD symptoms at 6 months as dependent variables).

To examine the role of cortisol, DHEAS and cortisol-to-DHEAS ratio in predicting a PTSD diagnosis at 6 weeks and 6 months, we performed logistic regression analyses with and without the above mentioned covariates.

To explore DHEAS's putative restorative effects, we performed a linear regression analysis of the contribution of

DHEAS, controlling for age and gender, to change in PTSD severity from 6 weeks to 6 months. PTSD change scores were computed by subtracting CAPS scores at 6 months from CAPS scores at 6 weeks.

All analyses were carried out in SPSS 19.0 with p-values $<.05$ indicating statistical significance.

3. Results

3.1. Participants

Of the 1496 eligible patients who presented at the trauma centers, 852 patients (57%) consented to participate in the ongoing prospective study of which blood samples of 397 patients (46.6%) were collected and analyzed. There were no differences between patients with and without collected blood samples in age, gender, marital status, educational background, country of origin, trauma history, traumatic event, ISS, GCS, time of day of initial medical assessment, or PTSD symptoms at 6 weeks or 6 months. Table 1 shows the sociodemographic and clinical characteristics of the 397 participants. The 6 week and 6 month assessments of PTSD symptoms took place at mean 52.3 days (SD = 26.0, n = 291, 73.3%) and 214.2 days (SD = 36.1, n = 226, 56.9%). Patients not assessed for PTSD at 6 months did not differ from those who were assessed on any of the before mentioned background or clinical characteristics. PTSD prevalence was 10.3% (n = 30) at 6 weeks and 6.2% (n = 14) at 6 months.

Table 1 Sociodemographic and clinical characteristics.

Characteristics	*N*	%
Male gender	253	63.7
Married or cohabitating	152	40.2
College or university degree	80	20.2
Country of origin: Netherlands	314	83.5
Traumatic event:		
Traffic accident	272	68.5
Fall from height	48	12.1
Work-related accident	43	10.8
Physical abuse	14	3.5
Other: fire, recreational, natural disaster, airplane crash	20	5.0
ICU admission	47	11.8
Time of blood sampling:		
Morning (0600–1200 h)	104	28.3
Afternoon (1200–1800 h)	132	35.9
Evening (1800–2400 h)	97	24.4
Night (2400–0600 h)	35	8.8
PTSD diagnosis at 6 weeks	30	10.3
PTSD diagnosis at 6 months	14	6.2

Characteristics	*M*	SD
Age in years	42.57	15.48
Trauma history	2.92	2.19
ISS	8.76	8.87
GCS	14.40	2.32
Plasma cortisol (nmol/L)	714.74	260.87
Plasma DHEA-S (nmol/L)	4.65	3.40
CAPS at 6 weeks	21.17	18.51
CAPS at 6 months	16.33	15.23

PTSD, posttraumatic stress disorder; ISS, injury severity score; GCS, Glasgow Coma Score; DHEA-S, dehydroepiandrosterone-sulfate; ICU, intensive care unit; CAPS, Clinician Administered PTSD Scale.

3.2. Univariate analyses of cortisol and DHEAS

Means and standard deviations for cortisol and DHEAS are displayed in Table 1. Compared to the reference values, cortisol levels were increased in 76% (n = 281) of patients and decreased in 1.4% (n = 5). DHEAS was increased in 6.5% (n = 5) and decreased in 24% (n = 91). Cortisol and DHEAS were positively correlated (r = .18, $p < .001$, n = 390). Cortisol (F (3,364) = 2.26, p = .08) and DHEAS levels (F (3,357) = 1.68, p = .17) were not significantly associated with time of day of blood sampling. Cortisol-to-DHEAS ratio, however, was significantly greater during the afternoon compared to evening (F (3,357) = 4.45, p = .004, mean difference = 81.42, SD = 29.80) and nighttime (mean difference = 133.51, SD = 41.85), indicating higher cortisol relative to lower DHEAS in the afternoon compared to lower cortisol versus higher DHEAS in the evening and night.

Patients who were older (r = .17, p = .001, n = 397), severely injured (ISS $\geq$ 16; t (341) = −5.04, $p < .001$), hospitalized (t (381) = −5.82, $p < .001$), and patients who were injured due to falling from a height (F (4,392) = 4.94, p = .001), had higher mean cortisol levels. DHEAS levels were negatively associated with age (r = −.39, $p < .001$, n = 390) and female gender (t (388) = 4.81, $p < .001$). Higher cortisol-to-DHEAS ratios were found for women than for men (t (388) = −3.62, $p < .001$) and for hospitalized versus non-hospitalized patients (t (374) = −2.16, p = .03). Cortisol-to-DHEAS ratio was positively correlated with age (r = .45, $p < .001$, n = 390).

3.3. Prediction of PTSD symptoms

Table 2 presents the predictive values of acute cortisol and DHEAS for 6 weeks and 6 months PTSD symptoms. Lower cortisol and higher DHEAS both significantly predicted PTSD symptoms at 6 weeks (model 1). At 6 months, only lower cortisol was a significant predictor of PTSD symptoms (model 3). Cortisol accounted for 2% of the total explained variance for 6-week PTSD symptoms in models 1 and 3. After controlling for the effects of age, gender, time of blood sampling, injury, trauma history, and ICU admission, lower cortisol remained a significant predictor for PTSD symptoms at 6 weeks (model 2) and 6 months (model 4), but DHEAS showed no effects. The outcomes of the models with cortisol-to-DHEAS ratio as a predictor are shown in Table 3. A smaller cortisol-to-DHEAS ratio significantly predicted PTSD symptoms at 6 weeks (model 5), but not anymore after inclusion of the covariates (model 6), and not at 6 months (models 7 and 8).

Logistic regression analyses for acute and chronic PTSD diagnoses showed no significant odd's ratios (OR) for cortisol

Table 2 Predictive values of acute cortisol and DHEAS for 6 week and 6 month PTSD symptoms with and without control variables.

	PTSD symptoms 6 weeks		PTSD symptoms 6 months	
	Model 1: R^2 = .03	Model 2: R^2 = .09	Model 3: R^2 = .01	Model 4: R^2 = .06
Cortisol	−.14**	−.15*	−.12*	−.16*
DHEAS	.12*	.10	.05	.05
Gender		.20**		.14*
Age		−.05		−.01
Morning		.04		.04
Evening		.12		.06
Night		.12		.08
ISS		.09		.12
Trauma history		.18*		.19**
ICU admission		−.02		−.03

PTSD, posttraumatic stress disorder; DHEAS, dehydroepiandrosterone-sulfate; ISS, injury severity score; ICU, intensive care unit.
N.B. Beta values of multivariate regression analyses of PTSD symptoms at 6 weeks and 6 months by cortisol and DHEAS with and without controlling for gender, age, time of blood sampling, injury severity score, trauma history, and ICU admission.
* $p < .05$.
** $p < .01$.

(6 weeks: OR = .98, 95% CI [.91—1.06], p = .68; 6 months: OR = .95, 95% CI [.87—1.03], p = .24), DHEAS (6 weeks: OR = 1.24, 95% CI [.76—2.00], p = .39; 6 months: OR = 1.04, 95% CI [.48—2.22], p = .93), or cortisol-to-DHEAS ratio (6 weeks: OR = .98, 95% CI [.92—1.04], p = .44; 6 months: OR = .98, 95% CI [.91—1.07], p = .69).

Lastly, change in PTSD symptoms between 6 weeks and 6 months was not significantly predicted by acute DHEAS, controlling for age and gender (β = .10, t = 1.47, p = .15; adjusted R^2 = .02, F (3,316) = 3.29, p = .03).

4. Discussion

This study showed that lower plasma cortisol levels in injured patients assessed at the trauma resuscitation room predicted acute and chronic PTSD symptoms, even after controlling for age, gender, time of blood sampling, injury, trauma history, and ICU admission. Higher acute DHEAS levels and a smaller cortisol-to-DHEAS ratio contributed to 6 week PTSD symptoms, but not after controlling for the same factors, and not at 6 months. There were no significant effects of cortisol, DHEAS or cortisol-to-DHEAS ratio on acute or chronic PTSD diagnoses. Lastly, DHEAS did not contribute significantly to PTSD symptom change between 6 weeks and 6 months.

In line with previous studies (Aardal-Eriksson et al., 2001; Delahanty et al., 2000; Ehring et al., 2008; McFarlane et al., 2011), our findings confirm the hypothesis that the development of PTSD may partly be explained by dysfunctioning of the HPA-axis. Moreover, we extended previous results by showing that cortisol is not only a predictor for acute PTSD symptoms, but continues to predict chronic PTSD symptoms at 6 months, even when controlling for relevant trauma and injury characteristics. As proposed, lower levels of circulating cortisol likely prolong the adrenergic response, thereby strengthening the consolidation of the fear memory (Yehuda, 2002). Recent research has also implicated cortisol in the expression of genes relevant to PTSD, such as FKBP5,

Table 3 Predictive values of acute cortisol-to-DHEAS ratio for 6 week and 6 month PTSD symptoms with and without control variables.

	PTSD symptoms 6 weeks		PTSD symptoms 6 months	
	Model 5: R^2 = .03	Model 6: R^2 = .09	Model 7: R^2 = .01	Model 8: R^2 = .05
Cortisol-to-DHEAS ratio	−.16**	−.13	−.10	−.11
Gender		.19**		.14*
Age		−.05		−.00
Morning		.04		.04
Evening		.12		.06
Night		.13		.08
ISS		.04		.06
Trauma history		.18**		.19**
ICU admission		.01		.01

PTSD, posttraumatic stress disorder; DHEAS, dehydroepiandrosterone-sulfate; ISS, injury severity score; ICU, intensive care unit.
N.B. Beta values of multivariate regression analyses of PTSD symptoms at 6 weeks and 6 months by cortisol-to-DHEAS ratio with and without controlling for gender, age, time of blood sampling, injury severity score, trauma history, and ICU admission.
* $p < .05$.
** $p < .01$.

neuropeptide-Y, and BDNF (see Zoladz and Diamond, 2013, for a review), which points to the necessity for a more comprehensive viewpoint of the influence of stress hormones in general, and cortisol in particular, in the onset of PTSD. As a biomarker for subsequent PTSD symptoms, acute cortisol levels in itself are an interesting target, as they are easily obtainable in injured populations seeking medical assistance and demonstrated a stable effect on acute and chronic PTSD symptoms in our study. However, it is still questionable to what extent acute cortisol levels could predict which individuals go on to develop or not develop PTSD (i.e., positive and negative predictive value), which pertains to the limited variance of PTSD severity explained by acute cortisol as found in our study. In addition, the RIA antibody method used to measure cortisol in our study also may have been suboptimal due to lack of specificity. A recent study using a standard cortisol radioimmunoassay suggested that low cortisol levels predicted poor treatment outcome, whereas use of a more accurate mass spectrometry methodology that measures cortisol and its metabolites separately showed that low levels of a reduced metabolite of cortisol produced by 5alpha reductase, rather than low cortisol, actually predicted poor outcome (Yehuda et al., 2009). Note that 5alpha reductase is also involved in the production of GABAergic reduced metabolite of progesterone (e.g. allopregnanolone) and testosterone (androsterone), both considered to have a conceivable role in PTSD risk (Gillespie et al., 2013).

To the best of our knowledge, our study was the first to investigate the role of DHEAS in the prediction of acute and chronic PTSD. In line with previous cross-sectional studies (Gill et al., 2008; Jogems-Kosterman et al., 2007; Yehuda et al., 2006), higher DHEAS and a smaller cortisol-to-DHEAS ratio were associated with PTSD symptoms at 6 weeks, although not after controlling for background and injury characteristics. Cross-sectional and longitudinal studies on DHEA(-S) and PTSD so far produced highly mixed results, which could indicate a dual effect or performance of DHEA(-S) in trauma-exposed people. This was found in one longitudinal study of refugees: over time, negative events were associated with increases in DHEAS in refugees with PTSD and with decreases in DHEAS levels in those without PTSD (Sondergaard and Theorell, 2003). Moreover, an interaction effect was found between PTSD and depression: in depressed subjects, lower DHEAS was found for PTSD versus non-PTSD, whereas in non-depressed subjects, higher DHEAS was found in PTSD versus non-PTSD (Sondergaard et al., 2002). As DHEA responses are more marked than DHEAS responses to acute stress (Lennartsson et al., 2012), it is possible that DHEA could have played a larger predictive role in our study than DHEAS did. More research is needed to determine the usefulness of DHEA versus DHEAS as a biomarker for subsequent PTSD symptomatology, for example in populations with a higher PTSD prevalence rate, such as victims of rape, combat or interpersonal violence.

This study is the first to show a predictive effect of plasma cortisol, whereas previous studies finding predictive effects for cortisol used saliva or urine samples (Aardal-Eriksson et al., 2001; Delahanty et al., 2000; Ehring et al., 2008; McFarlane et al., 2011). It is possible that our larger sample provided sufficient power for the analyses. Second, it is possible that the timing of our blood draw, within hours of the traumatic event for the entire participant sample, provided sufficient opportunity to witness the acute stress response of the survivors.

In our sample, all patients had endured a physical trauma with the possibility of severe injury. As in previous studies in similar populations (Delahanty et al., 2003; Woolf, 1992), injury severity was significantly positively correlated with acute cortisol levels. It is unclear to what extent our findings may be generalizable to populations without possible severe injury, such as victims of war or rape. However, since we included injury severity as a confounding variable in our analyses, our results show that acute cortisol was an independent predictor for consequent PTSD. Future studies should examine whether acute cortisol displays similar predictive effects on PTSD for injured versus non-injured trauma survivors.

Strengths of our study are that we included a relatively large sample of 397 injured patients, who were assessed at several occasions following trauma using clinical interviews. Limitations may be that blood samples were collected in only half of our originally included sample. A large proportion of blood samples were missing, most likely due to uninformed hospital staff, use of the blood samples for medical reasons or technical problems in conservation, preparation, transport or laboratory processing. Although our final sample did not differ from the larger sample with respect to baseline variables, selection bias cannot be ruled out. A similar concern is the attrition at follow-up of 22%. Further, although we collected and controlled for various important covariates, among which trauma history, injury severity and ICU admission, we did not account for other possible confounders, such as nicotine use, oral contraceptive use, experienced pain or alcohol or drug use at the time of blood sampling. Nicotine and oral contraceptives have been shown to suppress cortisol reactivity (Fu et al., 2007; Reynolds et al., 2013). Alternately, pain, alcohol and opiate drug use were found to increase the cortisol response to acute stress (Coventry et al., 2001; Ehring et al., 2008; Stankiewicz et al., 2013). Furthermore, studies have shown that smoking is an independent risk factor for mental health problems in a post-disaster sample (Olff et al., 2006; van der Velden et al., 2007), and pain moderates the relationship between cortisol and the development of PTSD in a sample of injury victims (Ehring et al., 2008). Since we had no information about these variables, we do not know whether they may have influenced the association between cortisol level and PTSD symptoms. Finally, we measured cortisol and DHEAS at only one occasion and had no information on day curves of stress hormones.

Future studies may be focused on elucidating whether low cortisol and increased DHEAS levels are pre-trauma vulnerability factors for PTSD or associated with the trauma. Moreover, while psychotherapy may be associated with restoring HPA-axis abnormalities (Olff et al., 2007), interventions targeting the HPA-axis more directly by glucocorticoid augmentation are promising (Yehuda et al., 2010). A recent pilot study on hydrocortisone administration immediately after trauma shows promise to the prevention of the development of PTSD (Zohar et al., 2011).

In summary, our study provides important new evidence on the crucial role of the HPA-axis in response to trauma by showing that cortisol and DHEAS levels predict PTSD symptoms in survivors of recent trauma.

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Conflict of interest statement

All authors declare that they have no financial interests or potential conflicts of interest.

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